UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/644,288	08/20/2003	Paul Diamond	PT100-3	5798

53255 7590 02/04/2009

PAUL DIAMOND
1605 JOHN STREET,
SUITE 102
FORT LEE, NJ 07024

EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
02/04/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/644,288	DIAMOND, PAUL	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/22/2008 has* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-21, 23, and 25-40* is/are pending in the application.

4a) Of the above claim(s) *1-16,21,23,26,28,31 and 33-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-20,25,27,29,30,32 and 36-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/22/2008 has been entered.

Claims 22 and 24 have been cancelled. Claims 1-16, 21, 23, 26, 28, 31, and 33-35 have been withdrawn. Claims 17, 18, 25, and 29 have been amended.

Claims 17-20, 25, 27, 29, 30, 32, and 36-40 are under examination.

2. Upon further considerations, the rejection of claims 17-20, 25, 27, 29, 30, 32, and 36-40 under 35 U.S.C. 103(a) as being unpatentable over Oliver et al. (U.S. Patent No. 5,723,765), in view of both Porter (Trends Genet, 1998, 14: 73-79, of record) and Angell et al. (EMBO J, 1997, 76: 3675-3684) is withdrawn in favor of a new rejection using a secondary reference which provides a better motivation to arrive at the claimed invention.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 17-20, 25, 27, 29, 30, 32, and 36-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Oliver et al. (U.S. Patent No. 5,723,765, of record), in view of both Peng et al. (Proc. Natl. Acad. Sci. USA, 1997, 94: 9261-8266) and Angell et al. (EMBO J, 1997, 76: 3675-3684, of record).

Oliver et al. teach a method of making a transgenic plant wherein excision of a pre-selected DNA sequence from the plant cellular genome is under external control (i.e., conditional excision); the transgenic plant is generated from a genetically modified plant cell comprising in its genome: (i) DNA sequences having a pre-selected gene linked to a pre-selected constitutively active promoter, wherein the gene and the promoter are separated by a blocking sequence flanked on each side by specific excision sequences, (ii) a gene encoding a recombinase which recognizes the specific excision sequences linked to a repressible promoter, and (iii) a gene encoding the repressor protein specific for the repressible promoter; the expression of the repressor protein being controlled by an outside stimulus, wherein the application of the stimulus blocks the repression of the recombinase leading to the excision of the excisable blocking sequence and brings the pre-selected gene under the control of the pre-selected promoter (claims 17, 18, 20, 25, 27, 29, 32, and 36-40) (Abstract; column 1, lines 58-67; column 2, lines 58-67; column 3, lines 1-67; column 4 ,lines 40-65; column 7, lines 7-20). Oliver et al. also teach that the blocking sequence may contain an

herbicide resistance gene, i.e., the excisable element comprises an expression cassette with a pre-selected gene (claims 19 and 30) (column 5, lines 30-32).

Although Oliver et al. teach controlling the expression of the repressor by an outside stimulus, they do not do not specifically teach an outside stimulus which results in the silencing of the mRNA encoding the repressor (claims 17, 18, 25, and 29). However, at the time the invention was made, providing outside stimuli resulting in silencing of target genes, wherein the outside stimuli are viral RNAs was taught by the prior art. For example, Peng et al. teach homology-dependent silencing of transgenes (i.e., pre-selected DNA) via modifying the transgenes such as to include part of a replicating plant viral RNA and infecting the plant cell comprising the transgene with the unmodified virus (Abstract; p. 8264, columns 1 and 2). Angell et al. teach that the homology-dependent method is a more reproducible approach for inducing conditional silencing in plants, as opposed to the other methods; they teach homology-dependent silencing of transgenes by using transgenes comprising a part of the replicating potato virus X (PVX) RNA and the viral double-stranded amplicon comprising the unmodified PVX (p. 3679, column 1, last paragraph, p. 3680, column 1, p. 3682, column 2, last paragraph). It would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Oliver et al. according to the teachings of Peng et al. and Angell et al. (i.e., using the more efficient homology-dependent silencing method) to achieve the predictable result of inactivating the repressor and cause the conditional excision of the pre-selected DNA from the plant genome.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments are answered below to the extent that they pertain to the instant rejection:

Applicant argues that, although the previous rejection for alleged obviousness over the combination of Oliver et al. in view of Porter was withdrawn in response to Applicant's amendments and remarks filed March 17, 2008, the Examiner still relies on Oliver for the teaching of the DNA excision elements (excision_system). Applicant notes that the Examiner relies on Angell et al. for teaching what is missing in Oliver et al. Applicant argues that the technology of Angell et al. on which the rejection relies in part is dramatically different from that utilized in the presently claimed invention and the present claims have also been amended to even more clearly distinguish the invention with respect to what is taught by Angell, as further explained below. Applicant submits that Angell et al. teach that modified or "unmodified" potato virus X (PVX) may be inserted into the genomic DNA of a plant under control of a plant promoter (CaMV 35S), so that a resulting (regenerated) transgenic plant transcribes from its genome replicative PVX (modified or unmodified). The genomically integrated replicating virus systems are referred to as "amplicons" in Angell. (Abstract, p. 3675, column 2, second paragraph). In the particular experiment to which the Examiner referred (p. 3679, column 1, last paragraph and FIG. 7), leaf fragments of a plant having a genomically integrated PVX amplicon (that gives rise to "unmodified" PVX dsRNA in cells) are bombarded (particle

bombardment technology) with transient expression constructs having the GUS reporter gene and 3' PVX sequence fragments. It was found that the PVX amplicon could silence GUS expression by virtue of the PVX sequences in the GUS reporter construct. Applicant notes that claims 17 and 18 already specify in each of their preambles that it is the excision construct that is present in and excisable from the cellular genome of the plants of these claims. While this limitation clearly distinguishes the claims over the cited prior art, Applicant nevertheless has amended these claims herein to recite the limitation within the body of each of claims 17 and 18, and similarly added this language to each of independent claims 25 and 29. In further distinguishing over the prior art by amendment, in independent method claims 17 and 25, the word "thereafter" has been added to more clearly specify that the plant having the genomically integrated DNA excision system is first provided, and thereafter unmodified viral dsRNA silences expression of the repressor protein to trigger excision. Applicant argues that, in the system of Angell et al., the plant cells are genetically modified so that PVX is genomically integrated in the plant cells and PVX is transcribed under control of a CaMV 35S promoter in said cells such that a replicating PVX results in the cells. While Angell et al. pose this situation as an "infection" of the cells, it is clear that this type of introduction of virus into the cells is not what is meant by "infecting" by the present application; paragraph 140 of corresponding Pub. No. 20040266708 clearly refers to "infection" in terms of entry into the cell when it states "when particular viruses, virus like agents or other environmental polynucleic acid molecules infect or otherwise enter or are produced in cells as a result of exposure to these agents in the environment."

Moreover, independent claim 17 already distinguishes over this aspect of Angell et al., when claim 17 literally recites "providing the viral double stranded RNA molecule into the plant cell" - this is not what is done in Angell et al. where DNA is introduced into the plant cells and integrated therewith and the cell itself thereafter expresses the viral dsRNA. Independent claims 18 and 25 similarly distinguish over this aspect of the rejection by specifying in the functional means-for language that the silencing is in response to the presence of the viral double stranded RNA molecule in the cell, i.e., not simply caused by the something already present but in response to something that occurs.

> (From Present Claim 18) means for causing RNA silencing against the mRNA transcript for the repressor protein in response to the presence in the cell of the unmodified viral double stranded RNA having the region of predetermined sequence so that expression of the site specific recombinase is derepressed thereby causing excision of the excisable sequence element

Applicant argues that the system of Angell et al. does not have or permits the same functionality of the presently claimed invention, nor does it solve the same problem or have the same advantages as now discussed. The system of Angell provides a plant wherein the cells are expressing active replicating virus from the cellular genomes. If a target having complementarity to the PVX virus enters the cell of Angell et al., such as the GUS reporter construct, that target will be silenced. The presently claimed invention provides system/methods wherein what will be the target of silencing, i.e., the repressor of the DNA excision system, is integrated (along with the whole excision system) into the plant genome, while the virus that can trigger the silencing that leads to excision is not integrated into the plant cellular genome. As

explained previously, by modifying the sequence of the repressor of the excision system to have complementarily to unmodified viral dsRNA sequence this permits conditional excision of a pre-selected DNA sequence from the plant genome in response to infection of the plant cells by the virus having said sequence. This same kind of conditionality is neither taught nor suggested by Angell et al. or the other cited references. To further facilitate allowance, the independent claims have also been amended herein to explicitly recite the conditionality of the excision. Where "conditionally" now appears in the preambles of the independent claims, it is pointed out that this limitation breathes life and meaning into the claims and should therefore be accorded patentable weight as it is a basis on which the claims are distinguished over the presently cited prior art. Applicant argues that in contrast, the system of Angell et al. is just a system where replicating amplicons, which give rise to siRNA, are "always on" in the plant cells. Moreover, Applicant argues, it should also be pointed out that from a safety perspective, it would be completely undesirable to place a plant such as from Angell et al. which drives expression of a replicating virus into the environment or any real world situation, e.g., to avoid recombination with other viruses in the environment. In contrast, the cells of the presently claimed invention do not have genomes driving expression of replicating viruses, nor could it be reasonably concluded that they do. Accordingly, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged however, they are not found persuasive for the following reasons:

Regarding Oliver et al., Applicant only notes that, although the previous rejection over the combination of Oliver et al. and Porter was previously withdrawn, the Examiner still relies on Oliver et al. in rejecting the instant claims. In response, it is noted that the rejection was withdrawn because, in the reply filed on 03/17/2008, Applicant amended the claims to recite the limitation that the gene encoding the repressor "is modified to contain at least one region of complementarity with a strand of the viral double-stranded RNA molecule"; such a limitation is not taught by the combination of Oliver et al. and Porter. Therefore, the Examiner properly withdrew the rejection. However, this does not mean that Oliver et al. cannot be applied in combination with secondary references teaching the new limitation (i.e., Angell et al). The teachings of Oliver et al. are still applicable (see the rejection above). Applicant did not provide any argument or evidence to demonstrate that the teachings of Oliver et al. do not pertain to the instant rejection. All of Applicant's arguments are directed to Angell et al. Applicant argues that, since the method of Angell is dramatically different from the claimed method, the rejection should be withdrawn. In response to this argument it is noted that Applicant cannot show nonobviousness by attacking Angell et al. individually where the rejection is based on a combination of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is the combination of Oliver et al., Peng et al., and Angell et al. which renders the claimed invention *prima facie* obvious. Except for the limitation of silencing the gene encoding the repressor, the primary reference (i.e., Oliver et al.) teaches all claim limitations (including first providing the transgenic plant and thereafter providing the an

outside stimulus, i.e., conditional excision). The missing limitation is taught by Peng et al. and Angell et al. With respect to Angell et al., they teach the concept that transgenes carrying regions of complementarity to a viral double-stranded RNAs are silenced when the viral double-stranded RNA is present in the same cell; they also teach such method as the most efficient approach for activating gene silencing. The argument that, in Angell et al., the amplicon is already inside the cell and the cell itself expresses the amplicon is not found persuasive. It would have been within the capabilities of one of skill in the art to extrapolate the teachings of Angell et al. to the method of Oliver et al.; using homology-dependent silencing of transgenes by first providing the transgenic plant cells and then the virus is taught by the prior art (see the teachings of Peng et al. above). Based on the teachings in the art as a whole, one of skill in the art would know how to substitute the outside stimulus of Oliver et al. with another outside stimulus in the form of a double-stranded viral RNA. By using the combined teachings above, one of skill in the art would have used a method wherein both the repressor of the DNA excision systems and the whole excision system are integrated into the plant cellular genome, wherein the sequence of the repressor has regions complementary to the unmodified viral dsRNA thus permitting its silencing and conditional excision of the pre-selected DNA in response to infection by the cognate virus. Therefore, it is the combination of all references above (and not Angell et al. alone) which renders the claimed invention *prima facie* obvious.

5. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ileana Popa/
Examiner, Art Unit 1633